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- ☒ [X] patent application of
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☐ [] divisional patent application of
☐ [] continuation-in-part patent application of

Inventor(s)/Applicant Identifier: Leping Li, Julio Cesar Medina, Bei Shan

For: LXR MODULATORS

☒ [X] This application claims priority from each of the following Application Nos./filing dates:

Provisional Patent Application No. 60/115,292, filed January 8, 1999

the disclosure(s) of which is (are) incorporated by reference.

Enclosed are:

- ☒ [X] 25 page(s) of specification
☒ [X] 4 page(s) of claims
☒ [X] 1 page of Abstract
 sheet(s) of ☐ [] formal ☐ [] informal drawing(s).

An assignment of the invention to _____

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A Power of Attorney by Assignee with Certificate Under 37 CFR Section 3.73(b).

A verified statement to establish small entity status under 37 CFR 1.9 and 37 CFR 1.27 ☐ [] is enclosed ☒ [X] was filed in the prior application and small entity status is still proper and desired.

A certified copy of a _____ application.

Information Disclosure Statement under 37 CFR 1.97.

A petition to extend time to respond in the parent application.

Notification of change of ☐ [] power of attorney ☐ [] correspondence address filed in prior application.

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United States Patent Application

LXR MODULATORS

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LXR MODULATORS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Serial No. 60/115,292, filed January 8, 1999, the contents of which are incorporated herein by reference.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

The invention described herein was not made with the aid of any federally sponsored grants.

FIELD OF THE INVENTION

The present invention relates to compounds and methods useful for the modulation of LXR and to compositions which modulate the activity of LXR. In view of the activity of LXR in the control of cholesterol homeostasis, the compounds described herein are useful for lowering plasma cholesterol levels.

BACKGROUND

Cholesterol is used for the synthesis of bile acids in the liver, the manufacture and repair of cell membranes, and the synthesis of steroid hormones. There are both exogenous and endogenous sources of cholesterol. The average American consumes about 450 mg of cholesterol each day and produces an additional 500 to 1,000 mg in the liver and other tissues. Another source is the 500 to 1,000 mg of biliary cholesterol that is secreted into the intestine daily; about 50 percent is reabsorbed (enterohepatic circulation). Excess accumulation of cholesterol in the arterial walls can result in atherosclerosis which is characterized by plaque formation. The plaques inhibit blood flow and promote clot formation, and can ultimately cause heart attacks, stroke and claudication. Development of therapeutic agents for the treatment of atherosclerosis and other diseases associated with cholesterol metabolism has been focused on achieving a more complete understanding of the biochemical pathways involved. Most recently, liver X receptors (LXRs) were identified as key components in cholesterol homeostasis.

The LXRs were first identified as orphan members of the nuclear receptor superfamily whose ligands and functions were unknown. Two LXR

proteins α and β are known to exist in mammals. The expression of LXR α is restricted, with the highest levels being found in the liver, and lower levels found in kidney, intestine, spleen, and adrenals. See, Willy, *et al.*, *Genes Dev.* **9**(9):1033-45 (1995). LXR β is rather ubiquitous, being found in nearly all tissues examined.

5 Recent studies on the LXRs indicate that they are activated by certain naturally occurring, oxidized derivatives of cholesterol, including 22(R)-hydroxycholesterol, 24(S)-hydroxycholesterol, and 24,25(S)-epoxycholesterol. See, Lehmann, *et al.*, *J. Biol. Chem.* **272**(6):3137-3140 (1997). The expression pattern of LXRs and their oxysterol ligands provided the first hint that these receptors may play a role in

10 cholesterol metabolism. See, Janowski, *et al.*, *Nature* **383**:728-731 (1996).

As noted above, cholesterol metabolism in mammals occurs via conversion into steroid hormones or bile acids. The role of LXRs in cholesterol homeostasis was first postulated to involve the pathway of bile acid synthesis, in which cholesterol 7 α -hydroxylase (CYP7 α) operates in a rate-limiting manner.

15 Support for this proposal was provided when additional experiments found that the CYP7 α promoter contained a functional LXR response element that could be activated by RXR/LXR heterodimers in an oxysterol- and retinoid-dependent manner.

Confirmation of LXR function as a transcriptional control point in cholesterol metabolism was made using knockout mice, particularly those lacking LXR α . See, Peet, *et al.*, *Cell* **93**:693-704 (1998). Mice lacking the receptor LXR α (*e.g.*, knockout or (-/-) mice) lost their ability to respond normally to increases in dietary cholesterol and were unable to tolerate any cholesterol in excess of that synthesized *de novo*. LXR α (-/-) mice did not induce transcription of the gene

20 encoding CYP7 α when fed diets containing additional cholesterol. This resulted in an accumulation of large amounts of cholesterol in the livers of LXR α (-/-) mice, and impaired hepatic function. These results further established the role of LXR α as the essential regulatory component of cholesterol homeostasis. LXR α is also believed to be involved in fatty acid synthesis. Accordingly, regulation of LXR α

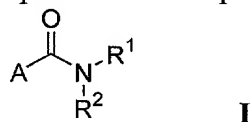
25 (*e.g.*, use of LXR α antagonists) could provide treatment for a variety of lipid disorders including obesity and diabetes.

In view of the importance of LXRs, and particularly LXR α to the delicate balance of cholesterol metabolism and fatty acid biosynthesis, we describe modulators of LXRs which are useful as therapeutic agents or diagnostic agents for

35 the treatment of disorders associated with bile acid and cholesterol metabolism, including cholesterol gallstones, atherosclerosis, lipid storage diseases, obesity, and diabetes. The agents described herein are also useful for disease states associated with serum hypercholesterolemia, such as coronary heart disease.

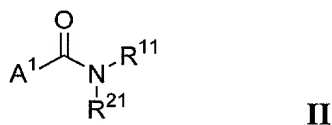
SUMMARY OF THE INVENTION

In one aspect, the present invention provides compositions for modulation of LXR α function in a cell. The compositions typically comprise a pharmaceutically acceptable excipient and a compound having the formula:



or a pharmaceutically acceptable salt thereof, in which the letter A represents substituted or unsubstituted forms of (C₅-C₁₈)alkyl or (C₅-C₁₈)heteroalkyl; the symbol R¹ represents substituted or unsubstituted forms of (C₃-C₁₂)alkyl, (C₃-C₁₂)heteroalkyl, aryl, heteroaryl, aryl(C₁-C₈)alkyl, heteroaryl(C₁-C₈)alkyl, aryl(C₂-C₈)heteroalkyl or heteroaryl(C₂-C₈)heteroalkyl; and the symbol R² represents substituted or unsubstituted forms of aryl, heteroaryl, aryl(C₁-C₈)alkyl, heteroaryl(C₁-C₈)alkyl, aryl(C₂-C₈)heteroalkyl or heteroaryl(C₂-C₈)heteroalkyl. Optionally, R¹ and R² are combined with the nitrogen atom to which each is attached, to form a 5-, 6-, 7- or 8-membered ring. Preferred compositions are those in which the compound above binds to the ligand binding domain of LXR α with an affinity of at least 1 micromolar.

A number of the compounds used in the present compositions are novel. Accordingly, the present invention provides, in another aspect, compounds having the formula:



or a pharmaceutically acceptable salt thereof, wherein the symbol A¹ represents substituted or unsubstituted forms of (C₅-C₁₂)monocycloalkyl, (C₅-C₁₂)heteromonocycloalkyl, (C₈-C₁₈)bicycloalkyl, (C₈-C₁₈)tricycloalkyl, (C₈-C₁₈)heterobicycloalkyl or (C₈-C₁₈)heterotricycloalkyl. The symbol R¹¹ represents substituted or unsubstituted forms of (C₃-C₁₂)alkyl, aryl, aryl(C₁-C₈)alkyl, aryl(C₂-C₈)heteroalkyl, (C₃-C₁₂)heteroalkyl, heteroaryl, heteroaryl(C₁-C₈)alkyl or heteroaryl(C₂-C₈)heteroalkyl. The symbol R²¹ represents substituted or unsubstituted forms of an aryl, heteroaryl, aryl(C₁-C₈)alkyl, aryl(C₂-C₈)heteroalkyl, heteroaryl(C₁-C₈)alkyl or heteroaryl(C₂-C₈)heteroalkyl group. Additionally, R¹¹ and R²¹ can be combined with the nitrogen atom to which each is attached to form a five- to eight-membered ring, with the following provisos:

when R²¹ is 2-pyridyl, R¹¹ is other than a substituted or unsubstituted 2-(1-piperazinyl)ethyl or (tetrahydro-2H-pyrido[3,4-b]indol-2-yl)ethyl group;

when R²¹ is substituted or unsubstituted phenyl, R¹¹ and R²¹ are not combined to form a ring with the attached nitrogen atom; and

when R²¹ is substituted or unsubstituted phenyl, R¹¹ is not allyl, 2-(acylamino)ethyl, or benzyloxycarbonyl.

In yet another aspect, the present invention provides methods for modulating LXR α in a cell by administering to or contacting the cell with a composition containing a compound of Formula I above.

In still another aspect, the present invention provides methods for treating LXR α -responsive diseases by administering to a subject in need of such treatment, a composition containing a compound of Formula I. These methods are particularly useful for the treatment of pathology such as hypercholesterolemia, atherosclerosis, and hyperlipoproteinemia. In certain embodiments, the compound can be administered to the subject in combination with an additional hypercholesterolemic agent, for example, bile acid sequestrants, nicotinic acid, fibric acid derivatives or HMG CoA reductase inhibitors.

Certain compounds of the present invention are antiproliferative and can be used in compositions for treating diseases associated with abnormal cell proliferation (*e.g.*, cancer). Other diseases associated with an abnormally high level of cellular proliferation include restenosis, where vascular smooth muscle cells are involved, inflammatory disease states, where endothelial cells, inflammatory cells and glomerular cells are involved, myocardial infarction, where heart muscle cells are involved, glomerular nephritis, where kidney cells are involved, transplant rejection, where endothelial cells are involved, infectious diseases such as HIV infection and malaria, where certain immune cells and/or other infected cells are involved, and the like. Infectious and parasitic agents per se (*e.g.* bacteria, trypanosomes, fungi, *etc*) are also subject to selective proliferative control using the subject compositions and compounds.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain, or cyclic hydrocarbon radical, or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multi-radicals, having the number of carbon atoms designated (*i.e.* C₁-

C₁₀ means one to ten carbons). Examples of saturated hydrocarbon radicals include groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, (cyclohexyl)methyl, cyclopropylmethyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butenyl, and the higher homologs and isomers. The term “alkyl,” unless otherwise noted, is also meant to include those derivatives of alkyl defined in more detail below as “cycloalkyl” and “alkylene.” The term “alkylene” by itself or as part of another substituent means a divalent radical derived from an alkane, as exemplified by -CH₂CH₂CH₂CH₂-. Typically, an alkyl group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the present invention. A “lower alkyl” or “lower alkylene” is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms.

The term “alkoxy,” employed alone or in combination with other terms means, unless otherwise stated, an alkyl group, as defined above, connected to the remainder of the molecule via an oxygen atom, such as, for example, methoxy, ethoxy, 1-propoxy, 2-propoxy and the higher homologs and isomers.

The term “heteroalkyl,” by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, consisting of the stated number of carbon atoms and from one to three heteroatoms selected from the group consisting of O, N, Si and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S may be placed at any interior position of the heteroalkyl group. The heteroatom Si may be placed at any position of the heteroalkyl group, including the position at which the alkyl group is attached to the remainder of the molecule. Examples include -CH₂-CH₂-O-CH₃, -CH₂-CH₂-NH-CH₃, -CH₂-CH₂-N(CH₃)-CH₃, -CH₂-S-CH₂-CH₃, -CH₂-CH₂-S(O)-CH₃, -CH₂-CH₂-S(O)₂-CH₃, -CH=CH-O-CH₃, -Si(CH₃)₃, -CH₂-CH=N-OCH₃, and -CH=CH-N(CH₃)-CH₃. Up to two heteroatoms may be consecutive, such as, for example, -CH₂-NH-OCH₃ and -CH₂-O-Si(CH₃)₃. Also included in the term “heteroalkyl” are those radicals described in more detail below as “heteroalkylene” and “heterocycloalkyl.” The term “heteroalkylene” by itself or as part of another substituent means a divalent radical derived from heteroalkyl, as exemplified by -CH₂-CH₂-S-CH₂CH₂- and -CH₂-S-CH₂-CH₂-NH-CH₂-. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini.

Still further, for alkylene and heteroalkylene linking groups, as well as all other linking groups described herein, no specific orientation of the linking group is implied.

The terms “cycloalkyl” and “heterocycloalkyl”, by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of “alkyl” and “heteroalkyl”, respectively. The terms “cycloalkyl” and “heterocycloalkyl” are also meant to include bicyclic, tricyclic and polycyclic versions thereof. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, adamantyl, and the like. Examples of heterocycloalkyl include 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, 1,4-diazabicyclo[2.2.2]oct-2-yl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like.

The terms “halo” or “halogen,” by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as “fluoroalkyl,” are meant to include monofluoroalkyl and polyfluoroalkyl.

The term “aryl,” employed alone or in combination with other terms (*e.g.*, aryloxy, arylthioxy, arylalkyl) means, unless otherwise stated, an aromatic substituent which can be a single ring or multiple rings (up to three rings) which are fused together or linked covalently. The rings may each contain from zero to four heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. The aryl groups that contain heteroatoms may be referred to as “heteroaryl” and can be attached to the remainder of the molecule through a carbon atom or a heteroatom. Non-limiting examples of aryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxaliny, 5-quinoxaliny, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl ring systems are selected from the group of acceptable substituents described below.

The terms “arylalkyl” and “arylheteroalkyl” are meant to include those radicals in which an aryl group is attached to an alkyl group (*e.g.*, benzyl, phenethyl, pyridylmethyl and the like) or a heteroalkyl group (*e.g.*, phenoxymethyl, 2-pyridyloxymethyl, 1-naphthyloxy-3-propyl, and the like). The arylalkyl and

arylheteroalkyl groups will typically contain from 1 to 3 aryl moieties attached to the alkyl or heteroalkyl portion by a covalent bond or by fusing the ring to, for example, a cycloalkyl or heterocycloalkyl group. For arylheteroalkyl groups, a heteroatom can occupy the position at which the group is attached to the remainder of the molecule.

For example, the term "arylheteroalkyl" is meant to include benzyloxy, 2-phenylethoxy, phenethylamine, and the like.

Each of the above terms (*e.g.*, "alkyl," "heteroalkyl" and "aryl") are meant to include both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be a variety of groups selected from: -OR', =O, =NR', =N-OR', -NR'R'', -SR', -halogen, -SiR'R''R''', -OC(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR''C(O)₂R', -NH-C(NH₂)=NH, -NR'C(NH₂)=NH, -NH-C(NH₂)=NR', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -CN and -NO₂ in a number ranging from zero to (2N+1), where N is the total number of carbon atoms in such radical. R', R'' and R''' each independently refer to hydrogen, unsubstituted(C₁-C₈)alkyl and heteroalkyl, unsubstituted aryl, aryl substituted with 1-3 halogens, unsubstituted alkyl, alkoxy or thioalkoxy groups, or aryl-(C₁-C₄)alkyl groups. When R' and R'' are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 5-, 6-, or 7-membered ring. For example, -NR'R'' is meant to include 1-pyrrolidinyl and 4-morpholinyl.

Similarly, substituents for the aryl groups are varied and are selected from: -halogen, -OR', -OC(O)R', -NR'R'', -SR', -R', -CN, -NO₂, -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR''C(O)₂R', -NH-C(NH₂)=NH, -NR'C(NH₂)=NH, -NH-C(NH₂)=NR', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -N₃, -CH(Ph)₂, perfluoro(C₁-C₄)alkoxy, and perfluoro(C₁-C₄)alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R' and R'' are independently selected from hydrogen, (C₁-C₈)alkyl and heteroalkyl, unsubstituted aryl, (unsubstituted aryl)-(C₁-C₄)alkyl, and (unsubstituted aryl)oxy-(C₁-C₄)alkyl.

Two of the substituents on adjacent atoms of the aryl ring may optionally be replaced with a substituent of the formula -T-C(O)-(CH₂)_q-U-, wherein T and U are independently -NH-, -O-, -CH₂- or a single bond, and q is an integer of from 0 to 2. Alternatively, two of the substituents on adjacent atoms of the aryl ring may optionally be replaced with a substituent of the formula -A-(CH₂)_r-B-, wherein A and B are independently -CH₂-, -O-, -NH-, -S-, -S(O)-, -S(O)₂-, -S(O)₂NR'- or a single bond, and r is an integer of from 1 to 3. One of the single bonds of the new ring so formed may

optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl ring may optionally be replaced with a substituent of the formula $-(CH_2)_s-X-(CH_2)_t-$, where s and t are independently integers of from 0 to 3, and X is $-O-$, $-NR'-$, $-S-$, $-S(O)-$, $-S(O)_2-$, or $-S(O)_2NR'-$. The substituent R' in $-NR'-$ and $-S(O)_2NR'-$ is selected from hydrogen or unsubstituted (C_1-C_6) alkyl.

As used herein, the term "heteroatom" is meant to include oxygen (O), nitrogen (N), sulfur (S) and silicon (Si).

The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, oxalic, maleic, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge, S.M., et al, "Pharmaceutical Salts", *Journal of Pharmaceutical Science*, **1977**, 66, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

In addition to salt forms, the present invention provides compounds which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide a compound of formula I. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme.

Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

Certain compounds of the present invention possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers and individual isomers are all intended to be encompassed within the scope of the present invention.

The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^3H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are intended to be encompassed within the scope of the present invention.

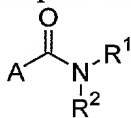
General

The present invention provides compositions, compounds and methods for modulating LXR α function in a cell. The compositions which are useful for this modulation will typically be those which contain an effective amount of an LXR α -modulating compound. In general, an effective amount of an LXR α -modulating compound is a concentration of the compound that will produce at 50 percent increase/decrease in LXR α activity in a cell-based reporter gene assay, or a biochemical peptide-sensor assay such as that described in co-pending applications Ser. Nos. 08/975,614 (filed November 21, 1997) and 09/163,713 (filed September 30, 1998).

Embodiments of the Invention

Compositions

In one aspect, the present invention provides compositions for modulation of LXR α function in a cell. The compositions typically comprise a pharmaceutically acceptable excipient and a compound having the formula:



I

or a pharmaceutically acceptable salt thereof, in which the letter A represents substituted or unsubstituted forms of (C₅-C₁₈)alkyl or (C₅-C₁₈)heteroalkyl. The symbol R¹ represents substituted or unsubstituted forms of (C₃-C₁₂)alkyl, aryl, aryl(C₁-C₈)alkyl, aryl(C₂-C₈)heteroalkyl, (C₃-C₁₂)heteroalkyl, heteroaryl, heteroaryl(C₁-C₈)alkyl or heteroaryl(C₂-C₈)heteroalkyl. The symbol R² represents substituted or unsubstituted forms of aryl, heteroaryl, aryl(C₁-C₈)alkyl, heteroaryl(C₁-C₈)alkyl, aryl(C₂-C₈)heteroalkyl or heteroaryl(C₂-C₈)heteroalkyl. Optionally, R¹ and R² can be combined with the nitrogen atom to which each is attached to form a 5-, 6-, 7- or 8-membered ring which may have from 0 to 2 additional heteroatoms as ring members. Examples of such rings include pyrrolidine, piperidine, morpholine, piperazine and the like. Preferred compositions are those in which the compound above binds to the ligand binding domain of LXR α with an affinity of at least 1 micromolar.

In certain preferred embodiments, A represents a substituted or unsubstituted form of a (C₅-C₁₈)cycloalkyl or a (C₅-C₁₈)heterocycloalkyl group, more preferably a (C₈-C₁₈)bicycloalkyl, (C₈-C₁₈)tricycloalkyl, (C₈-C₁₈)heterobicycloalkyl or (C₈-C₁₈)heterotricycloalkyl group. In particularly preferred embodiments, A represents a substituted or unsubstituted tricyclo[3.3.1.1^{3,7}]decanyl (or adamantyl), bicyclo[3.2.1]octanyl, bicyclo[5.2.0]nonanyl, bicyclo[4.3.2]undecanyl, tricyclo[2.2.1.0¹]heptanyl, tricyclo[5.3.1.1¹]dodecanyl, tricyclo[5.4.0.0^{2,9}]undecanyl, tricyclo[5.3.2.0^{4,9}]dodecanyl, tricyclo[4.4.1.1^{1,5}]dodecanyl or tricyclo[5.5.1.0^{3,11}]tridecanyl group. More preferably, A is a substituted or unsubstituted adamantyl group, most preferably an unsubstituted 1-adamantyl group.

Turning next to R¹, preferred embodiments are those in which R¹ is aryl(C₁-C₈)alkyl or heteroaryl(C₁-C₈)alkyl. More preferably, R¹ is branched heteroaryl(C₂-C₈)alkyl, for example, 1-(furan-2-yl)ethyl, 1-(pyridin-2-yl)ethyl, 1-(furan-2-yl)-2-propyl, 1-(2-pyridyl)-2-propyl, 1-(furan-2-yl)isobutyl, 1-(3-

pyridyl)isobutyl, 1-(pyridin-4-yl)ethyl, 1-(pyridin-4-yl)isobutyl, and the like. Most preferably, R^1 is 1-(furan-2-yl)ethyl or 1-(pyridin-2-yl)ethyl. In still other preferred embodiments, R^1 is a branched (C_3 - C_8)alkyl, more preferably an isopropyl group. In yet other preferred embodiments, R^1 is a heteroaryl(C_3 - C_8)alkenyl group. More preferably, R^1 is a 1-(3-furanyl)-3-butenyl group.

Returning to formula I above, the symbol R^2 is preferably a substituted or unsubstituted aryl or heteroaryl, more preferably a substituted or unsubstituted form of a pyridyl, phenyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, thiazolyl or furanyl group.

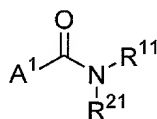
Still other preferred embodiments of the present compositions are those in which the compound of formula I has preferred combinations for A, R^1 and R^2 . In one preferred group of combinations, A is adamantyl and R^1 is aryl(C_1 - C_8)alkyl or heteroaryl(C_1 - C_8)alkyl. In another preferred group of compounds, A is adamantyl, R^1 is aryl(C_1 - C_8)alkyl or heteroaryl(C_1 - C_8)alkyl, and R^2 is aryl or heteroaryl. In yet another preferred group of combinations, A is adamantyl, R^1 is branched heteroaryl(C_2 - C_8)alkyl, and R^2 is aryl or heteroaryl. Still other preferred combinations are those in which A is adamantyl, R^1 is aryl(C_1 - C_8)alkyl or heteroaryl(C_1 - C_8)alkyl, and R^2 is pyridyl, phenyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, thiazolyl or furanyl.

Another group of preferred compounds for use in the present compositions are those in which A is substituted or unsubstituted adamantyl, R^1 is aryl(C_3 - C_8)alkenyl or heteroaryl(C_3 - C_8)alkenyl, and R^2 is a substituted or unsubstituted pyridyl or phenyl group. More preferably, the compounds are those in which A is unsubstituted 1-adamantyl, R^1 is phenyl(C_3 - C_8)alkenyl or furanyl(C_3 - C_8)alkenyl, and R^2 is a substituted or unsubstituted pyridyl or phenyl group. Most preferably, A is unsubstituted 1-adamantyl, R^1 is 1-(3-furanyl)-3-butenyl, and R^2 is a substituted or unsubstituted pyridyl or phenyl group. Preferred substituents for the phenyl or pyridyl group are small electron-withdrawing substituents, for example, halogen, halo(C_1 - C_3)alkyl, nitro, cyano, and the like.

In another group of preferred compounds for use in the present compositions, A is substituted or unsubstituted adamantyl, R^1 is branched (C_3 - C_8)alkyl, and R^2 is a substituted or unsubstituted pyridyl or phenyl group. More preferably, the compounds are those in which A is unsubstituted 1-adamantyl, R^1 is branched (C_3 - C_8)alkyl, and R^2 is a substituted or unsubstituted pyridyl or phenyl group. Most preferably, A is unsubstituted 1-adamantyl, R^1 is isopropyl, and R^2 is a substituted or unsubstituted pyridyl or phenyl group. Preferred substituents for the phenyl or pyridyl group are small electron-withdrawing substituents, for example, halogen, halo(C_1 - C_3)alkyl, nitro, cyano, and the like.

Compounds

A number of the compounds used in the present compositions are novel. Accordingly, the present invention provides, in another aspect, compounds having the formula:



II

or a pharmaceutically acceptable salt thereof, wherein the symbol A¹ represents substituted or unsubstituted forms of (C₅-C₁₂)monocycloalkyl, (C₅-C₁₂)heteromonocycloalkyl, (C₈-C₁₈)bicycloalkyl, (C₈-C₁₈)tricycloalkyl, (C₈-C₁₈)heterobicycloalkyl or (C₈-C₁₈)heterotricycloalkyl. The symbol R¹¹ represents substituted or unsubstituted forms of (C₃-C₁₂)alkyl, aryl, aryl(C₁-C₈)alkyl, aryl(C₂-C₈)heteroalkyl, (C₃-C₁₂)heteroalkyl, heteroaryl, heteroaryl(C₁-C₈)alkyl or heteroaryl(C₂-C₈)heteroalkyl. The symbol R²¹ represents an aryl, heteroaryl, aryl(C₁-C₈)alkyl, heteroaryl(C₁-C₈)alkyl, aryl(C₂-C₈)heteroalkyl or heteroaryl(C₂-C₈)heteroalkyl group. Additionally, R¹¹ and R²¹ can be combined with the nitrogen atom to which each is attached to form a five- to eight-membered ring, with the following provisos:

when R²¹ is 2-pyridyl, R¹¹ is other than a substituted or unsubstituted 2-(1-piperazinyl)ethyl or (tetrahydro-2H-pyrido[3,4-b]indol-2-yl)ethyl group;

when R²¹ is substituted or unsubstituted phenyl, R¹¹ and R²¹ are not combined to form a ring with the attached nitrogen atom; and

when R²¹ is substituted or unsubstituted phenyl, R¹¹ is not allyl, 2-(acylamino)ethyl, or benzyloxycarbonyl.

In formula II above, A¹ is preferably a substituted or unsubstituted form of (C₈-C₁₈)bicycloalkyl, (C₈-C₁₈)tricycloalkyl, (C₈-C₁₈)heterobicycloalkyl or (C₈-C₁₈)heterotricycloalkyl, more preferably, (C₈-C₁₈)tricycloalkyl or (C₈-C₁₈)heterotricycloalkyl. Still more preferably, A¹ is a substituted or unsubstituted form of (C₈-C₁₈)tricycloalkyl, with substituted or unsubstituted adamantyl being most preferred.

Preferred groups for R¹¹ are aryl(C₁-C₈)alkyl and heteroaryl(C₁-C₈)alkyl. More preferably, R¹¹ is branched heteroaryl(C₂-C₈)alkyl, for example, 1-(furan-2-yl)ethyl, 1-(pyridin-2-yl)ethyl, 1-(furan-2-yl)-2-propyl, 1-(2-pyridyl)-2-propyl, 1-(furan-2-yl)-3-propyl, 1-(3-pyridyl)isobutyl, 1-(pyridin-4-yl)ethyl, 1-(pyridin-4-yl)isobutyl, 1-(2-furanyl)-3-butenyl, 1-(3-furanyl)-3-butenyl and the like. Most preferably, R¹¹ is 1-(furan-2-yl)ethyl, 1-(3-furanyl)-3-butenyl or 1-(pyridin-2-yl)ethyl.

Preferred groups for R²¹ include aryl or heteroaryl, more preferably substituted or unsubstituted forms of pyridyl, phenyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, thiazolyl or furanyl.

As with the compounds used in the compositions above, certain combinations of substituents represent particularly preferred embodiments of the invention. For example, when A¹ is adamantyl, R¹¹ is preferably aryl(C₁-C₈)alkyl or heteroaryl(C₁-C₈)alkyl, and R²¹ is preferably aryl or heteroaryl. Still more preferred are those combinations in which R¹¹ is branched heteroaryl(C₂-C₈)alkyl, and R²¹ is aryl or heteroaryl. Still other preferred compounds are those in which A¹ is adamantyl, R¹¹ is aryl(C₁-C₈)alkyl or heteroaryl(C₁-C₈)alkyl, and R²¹ is pyridyl, phenyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, thiazolyl or furanyl.

Still other preferred compounds are those in which A¹ is substituted or unsubstituted adamantyl, R¹¹ is aryl(C₃-C₈)alkenyl or heteroaryl(C₃-C₈)alkenyl, and R²¹ is a substituted or unsubstituted pyridyl or phenyl group. More preferably, the compounds are those in which A¹ is unsubstituted 1-adamantyl, R¹¹ is phenyl(C₃-C₈)alkenyl or furanyl(C₃-C₈)alkenyl, and R²¹ is a substituted or unsubstituted pyridyl or phenyl group. Most preferably, A¹ is unsubstituted 1-adamantyl, R¹¹ is 1-(3-furanyl)-3-butenyl, and R²¹ is a substituted or unsubstituted pyridyl or phenyl group. Preferred substituents for the phenyl or pyridyl group are small electron-withdrawing substituents, for example, halogen, halo(C₁-C₃)alkyl, nitro, cyano, and the like.

In another group of preferred compounds for use in the present compositions, A¹ is substituted or unsubstituted adamantyl, R¹¹ is branched (C₃-C₈)alkyl, and R²¹ is a substituted or unsubstituted pyridyl or phenyl group. More preferably, the compounds are those in which A¹ is unsubstituted 1-adamantyl, R¹¹ is branched (C₃-C₈)alkyl, and R²¹ is a substituted or unsubstituted pyridyl or phenyl group. Most preferably, A¹ is unsubstituted 1-adamantyl, R¹¹ is isopropyl, and R²¹ is a substituted or unsubstituted pyridyl or phenyl group. Preferred substituents for the phenyl or pyridyl group are small electron-withdrawing substituents, for example, halogen, halo(C₁-C₃)alkyl, nitro, cyano, and the like.

Methods

In yet another aspect, the present invention provides methods for modulating the action of LXR α in a cell. According to this method, the cell is contacted with a sufficient concentration of a composition containing a compound of formula I, above, for either an agonistic or antagonistic effect to be detected.

In still another aspect, the present invention provides methods for the treatment of pathology such as hypercholesterolemia, atherosclerosis, and

hyperlipoproteinemia using pharmaceutical compositions containing compounds of the foregoing description of the general Formula I. Briefly, this aspect of the invention involves administering to a patient an effective formulation of one or more of the subject compositions. In other embodiments, the compound of Formula I can be administered in combination with other hypercholesterolemic agents (e.g., a bile acid sequestrant, nicotinic acid, fibric acid derivatives or HMG CoA reductase inhibitors), or in combination with other agents that affect cholesterol or lipid metabolism.

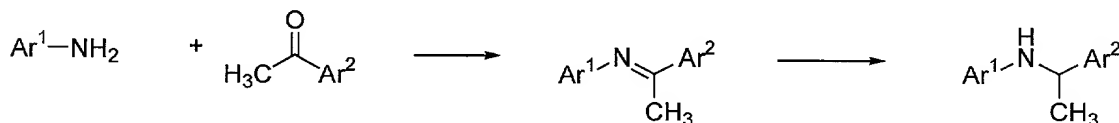
Preferred compounds and compositions for use in the present methods are those which have been described in the preceding sections.

Synthesis

Compounds of the present invention can be prepared using readily available starting materials or known intermediates. In general, the compounds are prepared from a carboxylic acid (or activated form thereof) of the formula A-CO₂H and a secondary amine of the formula R¹-NH-R² using known coupling procedures. A number of monocyclic, bicyclic and tricyclic alkane carboxylic acids are commercially available, including, for example, 1-adamantanecarboxylic acid, 3-noradamantanecarboxylic acid, 5-norbornene-2-carboxylic acid, and 1-methyl-1-cyclohexanecarboxylic acid.

Amines which are useful in forming the compound and compositions of the present invention are also readily accessible either through commercial sources or via chemical synthesis. For example, an arylamine (Ar¹-NH₂) can be condensed with an aryl ketone (e.g., CH₃C(O)Ar²) to yield an imine which can then be reduced to provide a suitable disubstituted amine (see Scheme 1). In some instances the intermediate imine can be converted to the amine *in situ*.

Scheme 1



One of skill in the art will understand that the above reaction scheme can also be used with, for example, nonaromatic amines and aldehydes or other ketones. An alternative method to the reductive amination procedure outlined above is described in the Examples section below.

Regardless of the source or procedure used to obtain a suitable amine component, coupling of the amine to an appropriate carboxylic acid, carboxylic acid

chloride, or activated ester is straightforward and can be accomplished using standard procedures.

Some of the compounds of Formula I may exist as stereoisomers, and the invention includes all active stereoisomeric forms of these compounds. In the case of optically active isomers, such compounds may be obtained from corresponding optically active precursors using the procedures described above or by resolving racemic mixtures. The resolution may be carried out using various techniques such as chromatography, repeated recrystallization of derived asymmetric salts, or derivatization, which techniques are well known to those of ordinary skill in the art.

The compounds of the invention may be labeled in a variety of ways. For example, the compounds may contain radioactive isotopes such as, for example, ^3H (tritium) and ^{14}C (carbon-14). Similarly, the compounds may be advantageously joined, covalently or noncovalently, directly or through a linker molecule, to a wide variety of other compounds, which may provide pro-drugs or function as carriers, labels, adjuvants, coactivators, stabilizers, *etc.* Such labeled and joined compounds are contemplated within the present invention.

Analysis of compounds

Representative compounds and compositions were demonstrated to have pharmacological activity in *in vitro* and cell culture assays, *e.g.*, they are capable of specifically modulating a cellular physiology to reduce an associated pathology or provide or enhance a prophylaxis.

Certain preferred compounds and compositions are capable of specifically regulating LXR α . Compounds may be evaluated *in vitro* for their ability to activate LXR α receptor function using cell-based assays such as that described in Lehmann, et al. (*J. Biol. Chem.* **1997**, 272(6), 3137-3140) or biochemical assays (see co-pending applications Ser. Nos. 08/975,614 (filed November 21, 1997) and 09/163,713 (filed September 30, 1998)). Alternatively, the compounds and compositions can be evaluated for their ability to increase or decrease gene expression modulated by LXR, using western-blot analysis. Established animal models to evaluate hypocholesterolemic effects of compounds are known in the art. For example, compounds disclosed herein can be tested for their ability to lower cholesterol levels in hamsters fed a high-cholesterol diet, using a protocol similar to that described in Spady et al. (*J. Clin. Invest.* **1988**, 81, 300), Evans et al. (*J. Lipid Res.* **1994**, 35, 1634), and Lin et al. (*J. Med. Chem.* **1995**, 38, 277). Still further, LXR α animal models (*e.g.*, LXR α (+/-) and (-/-) mice) can be used for evaluation of the present compounds and compositions (see, for example, Peet, et al. *Cell* **1998**, 93, 693-704).

Formulation and administration of compounds and pharmaceutical compositions

5 The invention provides methods of using the subject compounds and compositions to treat disease or provide medicinal prophylaxis, to activate LXR receptor function in a cell, to reduce blood cholesterol concentration in a host, to slow down and/or reduce the abnormal cellular proliferation including the growth of tumors, *etc.* These methods generally involve contacting the cell or cells with or administering to a host an effective amount of the subject compounds or pharmaceutically acceptable compositions.

10 The compositions and compounds of the invention and the pharmaceutically acceptable salts thereof can be administered in any effective way such as via oral, parenteral or topical routes. Generally, the compounds are administered in dosages ranging from about 2 mg up to about 2,000 mg per day, although variations will necessarily occur depending on the disease target, the patient, and the route of administration. Preferred dosages are administered orally in the range of about 0.05 mg/kg to about 20 mg/kg, more preferably in the range of about 0.05 mg/kg to about 2 mg/kg, most preferably in the range of about 0.05 mg/kg to about 0.2 mg per kg of body weight per day.

20 In one embodiment, the invention provides the subject compounds combined with a pharmaceutically acceptable excipient such as sterile saline or other medium, water, gelatin, an oil, *etc.* to form pharmaceutically acceptable compositions. The compositions and/or compounds may be administered alone or in combination with any convenient carrier, diluent, *etc.* and such administration may be provided in single or multiple dosages. Useful carriers include solid, semi-solid or liquid media including water and non-toxic organic solvents.

25 In another embodiment, the invention provides the subject compounds in the form of a pro-drug, which can be metabolically converted to the subject compound by the recipient host. A wide variety of pro-drug formulations are known in the art.

30 The compositions may be provided in any convenient form including tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, suppositories, *etc.* As such the compositions, in pharmaceutically acceptable dosage units or in bulk, may be incorporated into a wide variety of containers. For example, dosage units may be included in a variety of containers including capsules, pills, *etc.*

35 The compositions may be advantageously combined and/or used in combination with other hypocholesterolemic therapeutic or prophylactic agents, different from the subject compounds. In some instances, administration in conjunction with the subject compositions enhances the efficacy of such agents (i.e.,

there is a synergistic effect between the agents used in combination). Exemplary hypocholesterolemic and/or hypolipemic agents include: bile acid sequestrants such as quaternary amines (e.g. cholestyramine and colestipol); nicotinic acid and its derivatives; HMG-CoA reductase inhibitors such as mevastatin, pravastatin, and simvastatin; gemfibrozil and other fibric acids, such as clofibrate, fenofibrate, benzafibrate and cipo-fibrate; probucol; raloxifene and its derivatives; and mixtures thereof.

The compounds and compositions also find use in a variety of *in vitro* and *in vivo* assays, including diagnostic assays. For example, various allotypic LDL receptor gene expression processes may be distinguished in sensitivity assays with the subject compounds and compositions, or panels thereof. In certain assays and in *in vivo* distribution studies, it is desirable to use labeled versions of the subject compounds and compositions, e.g. radioligand displacement assays. Accordingly, the invention provides the subject compounds and compositions comprising a detectable label, which may be spectroscopic (e.g. fluorescent), radioactive, etc.

The following examples are offered by way of illustration and not by way of limitation.

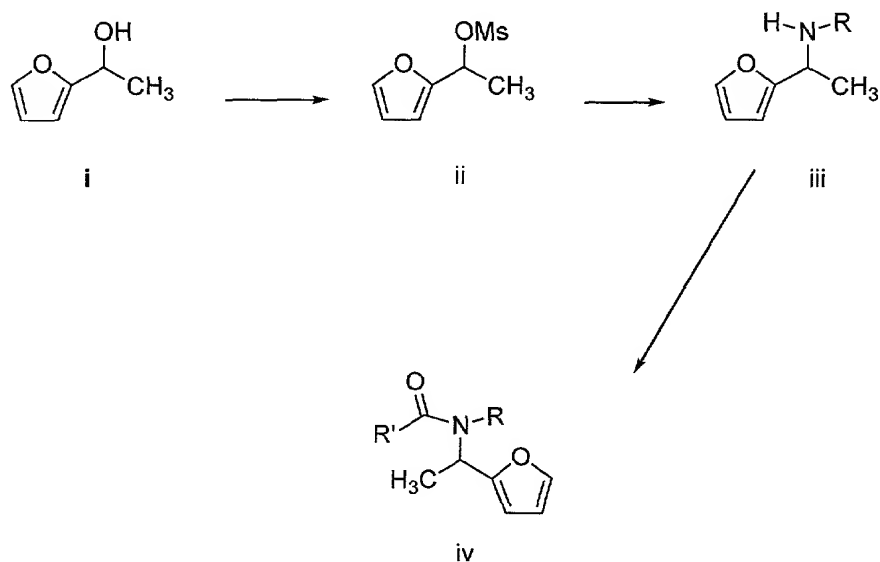
EXAMPLES

¹H-NMR spectra were recorded on a Varian Gemini 400 MHz NMR spectrometer. Significant peaks are tabulated in the order: number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br s, broad singlet) and coupling constant(s) in Hertz. Electron Ionization (EI) mass spectra were recorded on a Hewlett Packard 5989A mass spectrometer. Mass spectrometry results are reported as the ratio of mass over charge, followed by the relative abundance of each ion (in parentheses). Abbreviations used in the examples below have their accepted meanings in the chemical literature. For example, THF (tetrahydrofuran), LDA (lithium diisopropylamide), MeCN (acetonitrile), and DMAP (4-dimethylaminopyridine).

The compounds provided in Examples 1-8 were synthesized using the general scheme provided below (Scheme 2) for the preparation of 1-(2-furanyl)-ethylamine derivatives. The compounds provided in Examples 9 and 10 were prepared using similar methods. Suitable alteration of the various components in Scheme 2, including the secondary mesylate (ii), the amine used to displace the mesylate (to form iii), or the acyl chloride (used in the final step) provide entry into a wide variety of compounds of the present invention. As provided in the scheme, a suitable alcohol (i), preferably a primary or secondary alcohol, can be converted

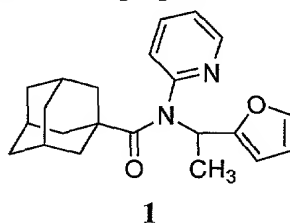
to a leaving group (e.g., a mesylate ester with the addition of methanesulfonylchloride) to provide an intermediate such as **ii**. Treatment of **ii** with a primary amine such as R-NH₂ provides the amine derivative **iii**. Subsequent acylation of the secondary amine functional group present in **iii** with acylating agents (R¹-COCl) provides the target compounds **iv**.

Scheme 2

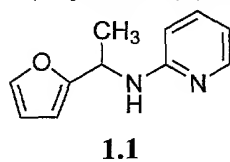


EXAMPLE 1

This example illustrates the preparation of Compound 1.



1.1 Preparation of intermediate 2-(1-(furan-2-yl)ethyl)aminopyridine (1.1)



(±)-1-(2-furyl)ethanol (10.8 g, 95.4 mmol) was dissolved in THF (264 mL) under N₂ at ambient temperature. To the mixture was added LDA (52.5 mL

of a 2.0 M solution in heptane/THF, 105 mmol, from Aldrich Chemical Co.) dropwise at -45°C (dry ice/MeCN bath) over a period of 12 min. The mixture was stirred at -45°C for 2 hours. Methanesulfonyl chloride (9.0 mL, 115 mmol) was added dropwise at -45°C for 10 min. The mixture was stirred at -45°C for 2 h, then a solution of 2-aminopyridine (15.7 g, 167 mmol) in THF (36ml) was added dropwise at -45°C over 15 min. The resulting mixture was quenched with water, extracted with CHCl₃, and the organic layer was washed with brine and dried over MgSO₄. The solvent was removed by evaporation and the crude product was purified by column chromatography on silica gel to afford the title compound as an oil in 51.8% yield.

¹H-NMR (CDCl₃ 400 MHz) δ 8.1 (d, J=4.76 Hz, 1H), 7.44-7.34 (m, 2H), 6.59 (dd, J=5.12, 7.2 Hz, 1H), 6.40 (d, J=8 Hz, 1H), 6.30 (m, 1H), 6.17 (d, J=3.16 Hz, 1H), 5.04 (m, 1H), 4.85 (m, 1H), 1.58 (d, J=6.64 Hz, 3H).

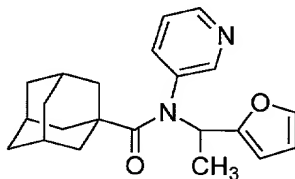
1.2 Preparation of Compound 1

To (1-furan-2-yl-ethyl)-pyridin-2-yl-amine (2.82 g, 15.0 mmol) in pyridine (24.2 mL) was added in one portion 1-adamantanecarbonyl chloride (9.40 g, 44.9 mmol) and DMAP (92 mg, 0.753 mmol) under N₂ at ambient temperature. The reaction mixture was heated to reflux for 1.5 h, then allowed to cool, quenched with H₂O, and extracted with CHCl₃. The organic layer was washed with brine and dried over MgSO₄. The solvent was evaporated and the crude product was purified by recrystallizing from ethyl acetate/ hexanes to afford 3.67 g of title compound.

¹H-NMR (CDCl₃, 400 MHz) δ 8.49 (m, 1H), 6.57 (d, J=7.96 Hz, 1H), 6.22 (d, J=1.89 Hz, 1H), 6.09 (m, 1H), 5.98 (m, 1H), 1.95-1.40 (m, 18H).

EXAMPLE 2

This example illustrates the preparation of Compound 2.



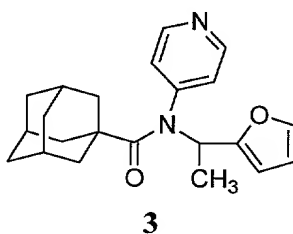
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The title compound was prepared in a manner analogous to that described for the compound of Example 1.

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 8.52 (d, $J=4.4$ Hz, 1H), 8.10 (br s, 1H), 7.35 (d, $J=1.8$ Hz, 1H), 7.20 (m, 1H), 7.05 (m, 1H), 6.22 (m, 2H), 5.93 (m, 1H), 1.84 (m, 2H), 1.72 (m, 6H), 1.56 (m, 3H), 1.45 (m, 3H), 1.34 (d, $J=7$ Hz, 3H).

EXAMPLE 3

This example illustrates the preparation of Compound 3.

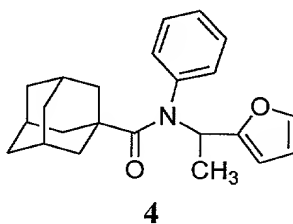


The title compound was prepared in a manner analogous to that described for the compound of Example 1.

$^1\text{H-NMR}$ (CDCl_3 , 400 MHz) δ 8.52 (d, $J=2$ Hz, 2H), 7.37 (s, 1H), 6.15 (m, 1H), 5.95 (d, $J=3.28$ Hz, 1H), 1.87–1.33 (m, 18H).

EXAMPLE 4

This example illustrates the preparation of Compound 4.

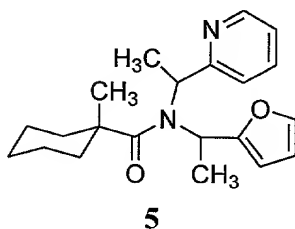


The title compound was prepared in a manner analogous to that described for the compound of Example 1.

$^1\text{H-NMR}$ (CDCl_3 , 400MHz) δ 7.34–7.20 (m, 5H), 6.8 (br s, 1H), 6.20 (m, 2H), 5.89 (m, 1H), 1.82–1.30 (m, 18H).

EXAMPLE 5

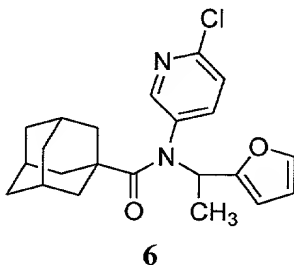
This example illustrates the preparation of Compound **5**.



The title compound was prepared in a manner analogous to that described for the compound of Example 1. ¹H-NMR (CDCl₃, 400 MHz) δ 8.49 (m, 1H), 7.52 (m, 1H), 7.35 (m, 1H), 7.20 (m, 1H), 6.57 (m, 1H) 6.23 (m, 1H), 6.15 (m, 1H), 6.00 (m, 1H), 1.90-0.80 (m, 16H).

EXAMPLE 6

This example illustrates the preparation of Compound **6**.

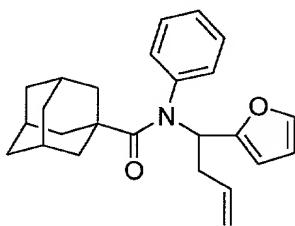


The title compound was prepared using methods outlined above.

¹H NMR (CDCl₃) δ 7.81 (broad s, 1H), 7.36 (s, 1H), 7.21 (d, J = 8.4 Hz, 1H), 6.95 (broad s, 1H), 6.21 (m, 2H), 5.95 (m, 1H), 1.88 (m, 3H), 1.70 (m, 6H), 1.60 (d, J=12 Hz, 3H), 1.48 (d, J=12 Hz, 3H), 1.33 (d, J=7 Hz, 3H). MS (ES⁺): 385 (M+H, 100). Anal. Calcd. for C₂₂H₂₅ClN₂O₂: C, 68.65; H, 6.55; N, 7.28; Cl, 9.21. Found: C, 68.37; H, 6.56; N, 7.18; Cl, 9.46.

EXAMPLE 7

This example illustrates the preparation of Compound 7.



7

Step 7a.

To a stirred solution of sodium dodecylsulfate (12 mL, 35 mM in water) and scandium trifluoromethanesulfonate [Sc(OTf)₃, 214 mg] were added aniline (0.19 mL, 2.06 mmol), allyltributylstannane (0.94 mL, 3.01 mmol), and 2-furaldehyde (0.215 mL, 2.59 mmol) successively, and the mixture was stirred at room temperature. After 24 h, the mixture was diluted with water and ethyl acetate. After separation of layers, the organic layer was washed with saturated NaHCO₃ twice, dried over MgSO₄, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel eluted with hexane/ethyl acetate (20:1) to give 0.360g of the desired homoallylic amine in 81.9% yield.

¹H NMR (CDCl₃) δ 7.35 (s, 1H), 7.15 (t, J = 6.8 Hz, 2H), 6.72 (t, J = 6.8 Hz, 1H), 6.61 (d, J = 6.8 Hz, 2H), 6.30 (d, J = 1.8 Hz, 1H), 6.18 (d, J = 1.8 Hz, 1H), 5.75 (m, 1H), 5.18 (d, J = 18 Hz, 1H), 5.12 (d, J = 10 Hz, 1H), 4.55 (m, 1H), 4.0 (bs, 1H), 2.66 (m, 1H).

Step 7b.

The mixture of 1-adamantanecarbonyl chloride (293 mg, 1.48 mmol), the above aniline (158 g, 0.74 mmol), 4-dimethylaminopyridine (DMAP, 30 mg, 0.25 mmol) in pyridine (2 mL) was heated at 90°C for 3 days. The reaction mixture was diluted with ethyl acetate, washed with 1 N HCl (2X) and brine. The organic layer was dried over MgSO₄, filtered and stripped. The crude product was purified by flash chromatography on silica gel eluted with hexane/ethyl acetate (20:1) to give 80 mg of the title compound in 28.8% yield (along with recovered starting aniline).

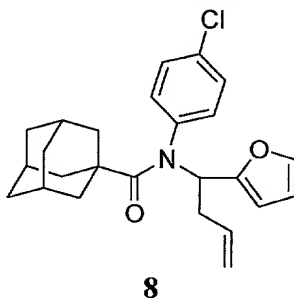
¹H NMR (CD₃OD) δ 7.44 (s, 1H), 7.35 (m, 2H), 6.90 (m, 2H), 6.25 (d, J = 4.8 Hz, 1H), 6.17 (t, J = 7.7 Hz, 2H), 5.99 (d, J = 4.8 Hz, 1H), 5.83 (m, 1H),

5.18 (d, $J = 18$ Hz, 1H), 5.06 (d, $J = 12$ Hz, 1H), 2.50 (t, $J = 4.8$ Hz, 2H), 1.79 (bs, 3H), 1.75 (d, $J = 12$ Hz, 3H), 1.68 (d, $J = 12$ Hz, 3H), 1.52 (d, $J = 12$ Hz, 3H), 1.43 (d, $J = 12$ Hz, 3H). MS (ES⁺): 376 (M+H, 100). Anal. Calcd. for C₂₅H₂₉NO₂: C, 79.96; H, 7.78; N, 3.73. Found: C, 79.79; H, 7.86; N, 3.62.

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EXAMPLE 8

This example illustrates the preparation of Compound 8.



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Step 8a:

Following the procedures described for Example 7 and substituting 4-chloroaniline for aniline, in Step 7a, the corresponding N-4-chlorophenylhomoallylamine was obtained, 0.448 g, 90.0%.

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¹H NMR (CDCl₃) δ 7.34 (s, 1H), 7.08 (d, $J = 6.8$ Hz, 2H), 6.52 (d, $J = 6.8$ Hz, 2H), 6.29 (d, $J = 3.2$ Hz, 1H), 6.13 (d, $J = 3.2$ Hz, 1H), 5.75 (m, 1H), 5.18 (d, $J = 18$ Hz, 1H), 5.13 (d, $J = 9.2$ Hz, 1H), 4.50 (m, 1H), 3.99 (bs, 1H), 2.64 (m, 2H).

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Step 8b:

Following conditions described in Step 7b and substituting the corresponding aniline with the 4-chlorosubstituted aniline from Step 8a, the title compound was obtained.

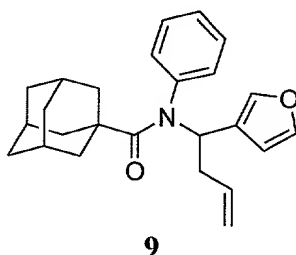
¹H NMR (CDCl₃) δ 7.30 (s, 1H), 7.00-7.30 (m, 4H), 6.21 (d, $J = 3.3$ Hz, 1H), 6.20 (t, $J = 4.8$ Hz, 1H), 5.95 (d, $J = 3.3$ Hz, 1H), 5.78 (m, 1H), 5.13 (d, $J = 18$ Hz, 1H), 5.08 (d, $J = 12$ Hz, 1H), 2.44 (m, 2H), 1.83 (bs, 3H), 1.73 (d, $J = 12$ Hz, 3H), 1.69 (d, $J = 12$ Hz, 3H), 1.56 (d, $J = 12$ Hz, 3H), 1.46 (d, $J = 12$ Hz, 3H). MS (ES⁺): 410 (M+H, 100). Anal. Calcd. for C₂₅H₂₈ClNO₂: C, 73.25; H, 6.88; N, 3.42. Found: C, 73.27; H, 6.94; N, 3.34.

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EXAMPLE 9

This example illustrates the preparation of Compound 9.



Step 9a:

Following the procedures described for Example 7 and substituting 3-furaldehyde for 2-furaldehyde in Step 7a, the corresponding 3-furylhomoallylamine was obtained, 0.32 g, 66.0% yield.

^1H NMR (CDCl_3) δ 7.35 (bs, 1H), 7.32 (s, 1H), 7.04 (t, $J = 7.2$ Hz, 2H), 6.70 (t, $J = 7.2$ Hz, 1H), 6.60 (d, $J = 7.2$ Hz, 2H), 6.36 (s, 1H), 5.80 (m, 1H), 5.16 (d, $J = 16$ Hz, 1H), 5.12 (d, $J = 12$ Hz, 1H), 4.48 (m, 1H), 3.90 (bs, 1H), 2.52 (m, 2H). MS (ES $^+$): 214 (M+H, 100).

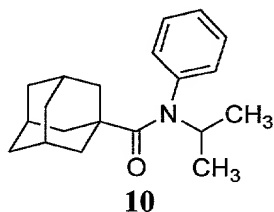
Step 9b:

Following conditions described in Step 7b and substituting the corresponding aniline with the aniline from Step 9a, the title compound was obtained in 28.3% yield.

^1H NMR (CDCl_3) δ 7.25-7.35 (m, 6H), 7.09 (s, 1H), 6.13 (s, 1H), 6.01 (t, $J = 6.0$ Hz, 1H), 5.80 (m, 1H), 5.11 (d, $J = 18$ Hz, 1H), 5.05 (d, $J = 12$ Hz, 1H), 2.51 (m, 1H), 2.35 (m, 1H), 1.79 (bs, 3H), 1.68 (bs, 6H), 1.54 (d, $J = 12$ Hz, 3H), 1.44 (d, $J = 12$ Hz, 3H). MS (ES $^+$): 376 (M+H, 100). Anal. Calcd. for $\text{C}_{25}\text{H}_{29}\text{NO}_2$: C, 79.96; H, 7.78; N, 3.73. Found: C, 79.89; H, 7.82; N, 3.72.

EXAMPLE 10

This example illustrates the preparation of Compound 10.



Following conditions described in Step 7b and substituting the aniline with isopropylamine, the title compound was obtained in 40% yield.

¹H NMR (CDCl₃) δ 7.35 (m, 3H), 7.11 (m, 2H), 4.92 (m, 1H), 1.79 (bs, 3H), 1.68 (bs, 6H), 1.53 (d, J = 12 Hz, 3H), 1.48 (d, J = 12 Hz, 3H), 0.98 (d, J = 6.8 Hz, 6H). MS (ES⁺): 298(M+H), 100.

EXAMPLE 11

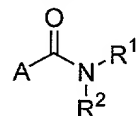
In order to identify agonists for LXR α , a cell-based high throughput screen was developed. Briefly, a DNA-binding domain of the nonreceptor transcription factor GAL4 was fused to the putative ligand-binding domain of LXR α . The resulting construct was introduced into 293 cells, together with an UAS-containing luciferase reporter construct. The transfected cells were then treated with the compounds and luciferase activity was measured. Individual compounds were evaluated relative to a control (no additional compound) at a concentration of 10 μ M. Relative luciferase activity is provided below for five of the compounds described in the Examples above (luciferase activity of the control was assigned a value of 1).

<u>Example</u>	<u>Relative Activity</u>
Example 1	4
Example 2	5
Example 3	≥ 10
Example 4	3
Example 5	≥ 10

All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

WHAT IS CLAIMED IS

1. A composition for modulation of LXR function in a cell, said composition comprising a pharmaceutically acceptable excipient and a compound having the formula:



or a pharmaceutically acceptable salt thereof, wherein

A is a member selected from the group consisting of (C₅-C₁₈)alkyl and (C₅-C₁₈)heteroalkyl;

R¹ is a member selected from the group consisting of (C₃-C₁₂)alkyl, aryl, aryl(C₁-C₈)alkyl, aryl(C₂-C₈)heteroalkyl, (C₃-C₁₂)heteroalkyl, heteroaryl, heteroaryl(C₁-C₈)alkyl and heteroaryl(C₂-C₈)heteroalkyl; and

R² is a member selected from the group consisting of aryl, heteroaryl, aryl(C₁-C₈)alkyl, heteroaryl(C₁-C₈)alkyl, aryl(C₂-C₈)heteroalkyl and heteroaryl(C₂-C₈)heteroalkyl;

wherein R¹ and R² are optionally combined together with the nitrogen atom to which each is attached to form a 5-, 6-, 7- or 8-membered ring, and said compound binds to the ligand binding domain of LXR α with an affinity of at least 1 micromolar.

2. A composition in accordance with claim 1, wherein A is selected from the group consisting of (C₅-C₁₈)cycloalkyl and (C₅-C₁₈)heterocycloalkyl.

3. A composition in accordance with claim 1, wherein A is selected from the group consisting of (C₈-C₁₈)bicycloalkyl, (C₈-C₁₈)tricycloalkyl, (C₈-C₁₈)heterobicycloalkyl and (C₈-C₁₈)heterotricycloalkyl.

4. A composition in accordance with claim 1, wherein A is adamantyl.

5. A composition in accordance with claim 3, wherein R¹ is selected from aryl(C₁-C₈)alkyl and heteroaryl(C₁-C₈)alkyl.

6. A composition in accordance with claim 3, wherein R² is selected from aryl and heteroaryl.

7. A composition in accordance with claim 1, wherein A is adamantyl, R¹ is selected from aryl(C₁-C₈)alkyl and heteroaryl(C₁-C₈)alkyl and R² is selected from aryl and heteroaryl.

8. A composition in accordance with claim 1, wherein A is adamantyl, R¹ is selected from heteroaryl(C₃-C₈)alkenyl and R² is selected from phenyl and pyridyl.

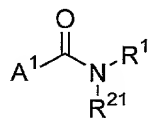
9. A composition in accordance with claim 1, wherein A is adamantyl, R¹ is selected from branched (C₃-C₈)alkyl and R² is selected from phenyl and pyridyl.

10. A composition in accordance with claim 1, wherein A is adamantyl, R¹ is heteroaryl(branched C₂-C₈)alkyl and R² is selected from aryl and heteroaryl.

11. A composition in accordance with claim 1, wherein A is adamantyl, R¹ is 1-(heteroaryl)-(C₂-C₈)alkyl and R² is selected from aryl and heteroaryl.

12. A composition in accordance with claim 1, wherein A is 1-adamantyl, R¹ is selected from aryl(C₁-C₈)alkyl and heteroaryl(C₁-C₈)alkyl, and R² is selected from pyridyl, phenyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, thiazolyl and furanyl.

13. A compound having the formula:



or a pharmaceutically acceptable salt thereof, wherein

A¹ is a member selected from the group consisting of (C₅-C₁₂)monocycloalkyl, (C₅-C₁₂)heteromonocycloalkyl, (C₈-C₁₈)bicycloalkyl, (C₈-C₁₈)tricycloalkyl, (C₈-C₁₈)heterobicycloalkyl and (C₈-C₁₈)heterotricycloalkyl;

R¹¹ is a member selected from the group consisting of (C₃-C₁₂)alkyl, aryl, aryl(C₁-C₈)alkyl, aryl(C₂-C₈)heteroalkyl, (C₃-C₁₂)heteroalkyl, heteroaryl, heteroaryl(C₁-C₈)alkyl and heteroaryl(C₂-C₈)heteroalkyl; and

R²¹ is a member selected from the group consisting of aryl, heteroaryl, aryl(C₁-C₈)alkyl, heteroaryl(C₁-C₈)alkyl, aryl(C₂-C₈)heteroalkyl and heteroaryl(C₂-C₈)heteroalkyl;

and wherein R¹¹ and R²¹ can be combined with the nitrogen atom to which each is attached to form a five- to eight-membered ring, with the following provisos:

when R²¹ is 2-pyridyl, R¹¹ is other than a substituted or unsubstituted 2-(1-piperazinyl)ethyl or (tetrahydro-2H-pyrido[3,4-b]indol-2-yl)ethyl group;

when R²¹ is substituted or unsubstituted phenyl, R¹¹ and R²¹ are not combined to form a ring with the attached nitrogen atom; and when R²¹ is substituted or unsubstituted phenyl, R¹¹ is not allyl, 2-(acylamino)ethyl, or benzyloxycarbonyl.

14. A compound in accordance with claim 13, wherein A¹ is selected from the group consisting of (C₈-C₁₈)bicycloalkyl, (C₈-C₁₈)tricycloalkyl, (C₈-C₁₈)heterobicycloalkyl and (C₈-C₁₈)heterotricycloalkyl.

15. A compound in accordance with claim 13, wherein A¹ is adamantyl.

16. A compound in accordance with claim 13, wherein R¹¹ is selected from aryl(C₁-C₈)alkyl and heteroaryl(C₁-C₈)alkyl.

17. A compound in accordance with claim 13, wherein R²¹ is selected from aryl and heteroaryl.

18. A compound in accordance with claim 13, wherein A¹ is adamantyl, R¹¹ is selected from aryl(C₁-C₈)alkyl and heteroaryl(C₁-C₈)alkyl and R²¹ is selected from aryl and heteroaryl.

19. A compound in accordance with claim 13, wherein A¹ is adamantyl, R¹¹ is selected from heteroaryl(C₃-C₈)alkenyl and R²¹ is selected from phenyl and pyridyl.

20. A compound in accordance with claim 13, wherein A¹ is adamantyl, R¹¹ is selected from branched (C₃-C₈)alkyl and R²¹ is selected from phenyl and pyridyl.

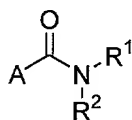
21. A compound in accordance with claim 13, wherein A¹ is adamantyl, R¹¹ is heteroaryl(branched C₂-C₈)alkyl and R²¹ is selected from aryl and heteroaryl.

22. A compound in accordance with claim 13, wherein A¹ is adamantyl, R¹¹ is 1-(heteroaryl)-(C₂-C₈)alkyl and R²¹ is selected from aryl and heteroaryl.

23. A compound in accordance with claim 13, wherein A¹ is 1-adamantyl, R¹¹ is selected from aryl(C₁-C₈)alkyl and heteroaryl(C₁-C₈)alkyl, and R²¹ is selected from pyridyl, phenyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, thiazolyl and furanyl.

24. A method for modulation of LXR in a cell, said method comprising administering to said cell a composition in accordance with claim 1.

1 **25.** A method for the treatment of LXR-responsive diseases, comprising
 2 administering to a subject in need of said treatment, a compound having the
 3 formula:



4
 5 or a pharmaceutically acceptable salt thereof, wherein

6 A is a member selected from the group consisting of (C₅-C₁₈)alkyl
 7 and (C₅-C₁₈)heteroalkyl;

8 R¹ is a member selected from the group consisting of (C₃-C₁₂)alkyl, aryl,
 9 aryl(C₁-C₈)alkyl, aryl(C₂-C₈)heteroalkyl, (C₃-C₁₂)heteroalkyl,
 10 heteroaryl, heteroaryl(C₁-C₈)alkyl and heteroaryl(C₂-C₈)heteroalkyl;
 11 and

12 R² is a member selected from the group consisting of aryl, heteroaryl,
 13 aryl(C₁-C₈)alkyl, heteroaryl(C₁-C₈)alkyl, aryl(C₂-C₈)heteroalkyl and
 14 heteroaryl(C₂-C₈)heteroalkyl;

15 wherein R¹ and R² are optionally combined together with the nitrogen atom to
 16 which each is attached to form a 5-, 6-, 7- or 8-membered ring, and said compound
 17 binds to the ligand binding domain of LXRα with an affinity of at least 1 micromolar.

1 **26.** A method in accordance with claim **25**, wherein said disease is selected
 2 from the group consisting of hypercholesterolemia and atherosclerosis or other
 3 disorders associated with bile acid and cholesterol metabolism.

1 **27.** A method in accordance with claim **25**, wherein said compound is
 2 administered in conjunction with an additional hypercholesterolemic agent selected
 3 from the group consisting of bile acid sequestrants, nicotinic acid, fibric acid
 4 derivatives and HMG CoA reductase inhibitors.

ABSTRACT OF THE INVENTION

The invention provides compounds, compositions and methods for modulating the effects of LXR α in a cell. The compounds and compositions are useful both as diagnostic indicators of LXR α function and as pharmacologically active agents. The compounds and compositions find particular use in the treatment of disease states associated with cholesterol metabolism, particularly atherosclerosis and hypercholesterolemia.

DECLARATION

As a below named inventor, I declare that:

My residence, post office address and citizenship are as stated below next to my name; I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: **LXR MODULATORS** the specification of which X is attached hereto or _____ was filed on _____ as Application No. _____ and was amended on _____ (if applicable).

I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56. I claim foreign priority benefits under Title 35, United States Code, Section 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Country	Application No.	Date of Filing	Priority Claimed Under 35 USC 119

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below:

Application No.	Filing Date
60/115,292	1/08/99

I claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application No.	Date of Filing	Status

Full Name of Inventor 1:	Last Name: LI	First Name: LEPING	Middle Name or Initial:	
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Full Name of Inventor 2:	Last Name: MEDINA	First Name: JULIO	Middle Name or Initial: CESAR	
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Full Name of Inventor 3:	Last Name: SHAN	First Name: BEI	Middle Name or Initial:	
Residence & Citizenship:	City: Redwood City	State/Foreign Country: California	Country of Citizenship: United States	
Post Office Address:	Post Office Address: 349 Quay Lane	City: Redwood City	State/Country: California	Postal Code: 94065

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signature of Inventor 1	Signature of Inventor 2	Signature of Inventor 3
<u>LEPING LI</u>	<u>JULIO CESAR MEDINA</u>	<u>BEI SHAN</u>
Date	Date	Date

SP 1056780 v1